REMARKS

Claims 31, 32, 41 and 50 have been amended to more particularly point out and distinctly claim the present invention. Specifically, these claims have been amended to include an additional limitation that "upon administration of said reagent said particles are dispersed in an aqueous medium and form a stable colloid." Support for this amendment is found in the description of preferred embodiments set forth on page 3, line 29 to page 4, line 2. Additional support for this limitation may also be found in the description of exemplary FullerTag nanocolloid suspensions on page 10, lines 3 to 8. No new matter has been added.

Claim 41 has been amended to more particularly point out and distinctly claim the present invention. Specifically, the claim has been amended to recite "at least an outer layer of said layers being chemically modified to provide improved chemical association of the modified layers with aqueous solution relative to non-modified layers, thereby forming a stable aqueous colloid." Support for this amendment is found in the description of preferred embodiments set forth at page 3, line 29 to page 4, line 2. No new matter has been added.

Claims 61 - 63 have been amended to more particularly point out and distinctly claim the present invention. Specifically, these claims have been amended to recite "wherein a surface of said particles is coated with a surfactant coating that increases the binding efficiency of said coated particles with fibrin relative to uncoated particles." Support for this amendment is found in the description of surfactant coated reagent particles set forth on page 6r, line 29 to page 7, line 2. Additional support for this limitation may also be found in the description of an exemplary embodiment, ThromboTrace, on page 10, lines 8 and 9. No new matter has been added.

New claims 64 -67 have been added to more particularly point out and distinctly claim the present invention. Support for these claims is found on page 2, lines 10 to 14.

In addition, support is found in the description of an exemplary nanocolloid suspension, FullerTag, on page 10, lines 4 to 8. No new matter has been added.

New claims 68 - 70 have been added to more particularly point out and distinctly claim the present invention. Support for these claims is found in the description of an exemplary embodiment, ThromboTrace, on page 10, lines 8 - 9. No new matter has been added.

The amendments and remarks as presented here are believed to place the case in condition for allowance. Accordingly, entry of these amendments, reconsideration of the Examiner's rejections and passage to allowance is respectfully requested. With this response claims 31 - 70 are pending.

The Rejections under 35 U.S.C. § 112, second paragraph

Claims 31, 32, 41, 42, 50, and 61-63 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter Applicants regard as the invention. Applicants traverse certain aspects of this rejection and have amended the claims in response to other aspects of this rejection.

The term "some" in claims 31, 32, 41 and 50 is allegedly vague and indefinite. Applicants maintain that, as used in the rejected claims, the term "some" clearly refers to a portion of the discrete particles of the present invention. To expedite prosecution and without acquiescing to this rejection, however, claims 31, 32, 41 and 50 have been amended to exclude reference to the allegedly vague term.

The term "fibrin-containing source" in claim 32 is alleged vague and indefinite. To expedite prosecution and without acquiescing to this rejection, the claim has been amended and now recites "a sample containing fibrin." Although Applicants maintain the previous recitation was clear, approval of the amended language is respectfully requested.

The term "stable" in claim 42 is alleged to be "relative, as there is no means to compare what stable or unstable means when recited in the context of the claims and specification." Applicants respectfully disagree with the examiner's interpretation of this term. In reference to a colloidal suspension, "stable" is a well known term of art signifying a physical state characterized by colloidal particles having an interface occupied by ions, molecules or both present in the medium they are dispersed in. A "stable" colloidal suspension refers to colloidal particles in which the interfacial layer of ions, molecules or both present in the medium substantially prevents aggregation of individual particles and subsequent precipitation. In the interest of expediting prosecution and without acquiescing to this rejection, claim 42 has been amended and now recites "at least an outer layer of said layers being chemically modified to provide improved chemical association of the modified layers with aqueous solution relative to non-modified layers, thereby forming a stable aqueous colloid."

The term "increases" in claims 61 - 63 is allegedly "a relative term which renders the claims indefinite." To expedite prosecution and without acquiescing to this rejection, claims 61 - 63 have been amended and now recite "wherein a surface of said particles is coated with a surfactant coating that increases the binding efficiency of said coated particles with fibrin relative to uncoated particles." Applicants submit that reference to "increases" in amended claims 61 - 63 is not indefinite because the amended claims clearly refer to increases in the binding efficiency of particles having a surfactant coating with fibrin relative to the binding efficiency of particles not having a surfactant coating with fibrin.

The Rejections under 35 U.S.C. § 103

Claims 31 - 63 have been rejected under Section 103 as allegedly unpatentable over Burch *et al.* (Nuc. Med. Communications) in view of Chignier *et al.* (Biomat.) in further view of Watson et al. (WO 93/15768) and Senden *et al.* (J. Nuc. Med.). Applicants have amended the rejected claims to more clearly specify the claimed invention and request reconsideration and withdrawal of the rejections in light of the following arguments.

The methods and reagents in the amended claims relate to stable diagnostic colloids comprising carbonaceous particles dispersed in aqueous media. Specifically, the physical and chemical properties of the carbonaceous particles of the present invention are selected to provide stable chemical association of the outer layer of each particle with an aqueous medium and effective, highly selective binding to fibrin. The combination of these physical and chemical properties provides for the diagnostic and drug-targeting function of the present invention. Amended claims 31 - 63 are not rendered unpatentable by the cited references because the combination of references fails to teach or suggest diagnostic particles capable of forming stable, aqueous colloids. Rather, the cumulative disclosure raised by the Examiner is limited to colloidal suspensions comprising non-aqueous particles dispersed in gaseous media.

Contrary to the Examiner's characterization, the particles described in Burch *et al.* **are not** "technetium-99m compounds in aqueous aerosols." While the diagnostic particles in Burch et al. are derived from a solution of sodium pertechnetate in normal saline, the reference teaches "evaporating [the solution] to dryness" in a graphite crucible at a "temperature of 2500° C in an atmosphere of pure argon." (see Burch *et al.*, pg. 866, lines 18 - 24). This interpretation of the composition of the particles disclosed in Burch *et al.* is confirmed by the Inventor's declaration shown in Exhibit A. Burch *et al.* does disclose diagnostic particles comprising "'soot', i.e. structured aggregates of carbon." However, the disclosed diagnostic reagents differ substantially from the colloids employed in the present invention. First, the carbonaceous particles in Burch *et al.* are suspended in an argon gas medium and, thus, are not capable of efficient delivery to aqueous samples containing soluble or insoluble fibrin. Second, the "soot" particles described in Burch *et al.* are not capable of stable association with aqueous media because of their highly aromatic character. Although "soot" may comprise a variety of forms, including graphite, glassy carbon, and fullerenic carbon, all of these carbonaceous materials rapidly aggregate into larger particles and precipitate out upon dispersion into an aqueous environment. Accordingly, Burch *et al.* does not disclose, enable or suggest stable colloidal suspensions comprising carbonaceous particles dispersed in aqueous media.

Although Burch *et al.* mentions use of "aqueous aerosols of technetium-99m compounds by Taplin and . . . colleagues," the cited references **do not** refer to carbonaceous particles or particles dispersed in aqueous media. Rather, the methods of the references cited by Burch *et al.* are limited to diagnostics comprising droplets of aqueous solution containing solvated technetium compounds. In contrast to the diagnostic colloids of the present inventions, these references describe colloids dispersed in gaseous media. Further, the diagnostic markers disclosed in these references comprise technetium solutes rather than technetium containing particles. Accordingly, the references cited by Burch *et al.* do not disclose, enable or suggest colloidal suspensions of particles dispersed in aqueous media or diagnostic preparations containing radiolabeled carbonaceous particles.

The distinction between the physical and chemical properties of the diagnostic colloids of the amended claims and those described in the cited references is substantial. First, the carbonaceous particles of the present invention are in their active form (i.e. bind to fibrin) in the aqueous phase. Unlike the particles in Burch *et al.*, therefore, the particles of the present invention are capable of targeting fibrin in a wide range of *in vivo* and *in vitro* aqueous settings, particularly physiological settings involving the circulation system. Second, the carbonaceous particles of the present invention are present as a stable colloid in the aqueous phase and, therefore, are capable of remaining in the aqueous phase for long times corresponding to long diagnostic observation times. In contrast, the diagnostic particles disclosed in Burch *et al.* tend to rapidly coagulate and precipitate upon dispersion into aqueous media. Third, modification the particles disclosed in Burch et al. to provide for stable association with an aqueous medium would have been well outside the grasp of the skilled artisan at the time of the invention because the aromatic carbon surface layers of such particles are extremely stable and highly hydrophobic.

To clarify the precise physical and chemical properties of the diagnostic colloids employed in the present invention, the claims have been amended to provide "upon administration of said reagent, said particles are dispersed in an aqueous medium and form

a stable colloid." The combination of references cited by the Examiner, including Burch *et al*, does not enable, disclose or suggest particles capable of forming a stable colloid in aqueous media. It is therefore submitted that no *prima facie* case of nonobviousness has been made out because the references, when combined, do not teach or suggest all the limitations appearing in the amended claims. MPEP § 706.02(j)

In addition, there is no suggestion or motivation in the combination of references to combine the diagnostic particles disclosed in Burch *et al.* with teachings relating to use of carbonaceous materials in aqueous environments. The Examiner characterizes Chignier *et al.* as teaching the "haemocompatibility and biological course of carbonaceous composites for cardiovascular devices." Without any motivation or suggestion to combine these teachings, however, there is insufficient teaching to enable a person of ordinary skill in the art at the time of the invention to integrate teachings related to cardiovascular implants to the diverse setting of colloidal diagnostics. Applicants submit that no prima facie case of nonobviousness has been made out because there is no suggestion or motivation to combine the teachings of the cited references. In re Vaeck, 947 F. 2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

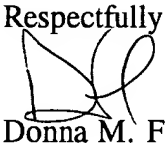
Moreover, the Burch *et al.* reference actually **teaches away** from the use of carbonaceous particles that form stable colloids in aqueous media. As described in the Inventor's declaration in Exhibit A, the express aim in Burch *et al.* is to provide gas-like diagnostic particles for imaging lung tissue, which do not suffer from the "many limitations" of aqueous radioactive tracers, (see, Burch *et al.*, pg, 866, lines 4 - 10 & pg. 867, lines 27 - 32). Such limitations include the loss of aqueous tracers across the blood-air barrier in the lung. Indeed, Burch *et al.* reports the benefits of non-aqueous radioactive tracers exhibiting no "clearance . . . from the lungs" and having long diagnostic half-lives. Since the Burch *et al.* reference teaches away from a limitation in the amended claims, it cannot serve as the basis of an obviousness rejection. Gillette Co. v. S.C. Johnson & Sons, Inc., 919 F.2d 720, 724, 16 U.S.P.Q2d 1923, 1927 (Fed. Cir. 1990).

CONCLUSION

In view of the foregoing arguments, this case is considered to be in condition for allowance and passage to issuance is respectfully requested. If there are any outstanding issues related to patentability, the courtesy of a telephone interview is requested, and the Examiner is invited to call to arrange a mutually convenient time.

This Amendment is accompanied by a Petition for Extension of Time and a check in the amount of $ 400.00, as required by 37 C.F.R. 1.17. Also enclosed is a check in the amount of $126.00 for the presentation of seven additional dependent claims, as required by 37 C.F.R. 1.16(c). If the amounts submitted are incorrect, please deduct the appropriate fee for this submission and any extension of time required from Deposit Account No. 07-1969.

Respectfully submitted,



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Marked up version of amended claim(s) in attached Amendment.

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31. (Once amended) A method for the *in vivo* detection of fibrin, said method comprising the steps of:

administering to said patient an effective amount of a detectable reagent comprising discrete particles dispersed in a pharmaceutically or veterinarily acceptable carrier, diluent, excipient, adjuvant or any combination thereof, wherein [at least some of] said particles comprise a detectable marker encased in at least two layers of carbon, wherein upon administration of said reagent said particles are dispersed in an aqueous medium and form a stable colloid;

binding [at least some of] said particles to said fibrin; and

detecting the presence of said detectable marker in said patient.

32. (Once amended) A method for the detection of fibrin in a [fibrin-containing source] a sample containing fibrin, said method comprising the steps of:

supplying to said [fibrin-containing source] sample containing fibrin a detectable reagent comprising discrete particles dispersed in a carrier, diluent, excipient, adjuvant or any combination thereof, wherein [at least some of] said particles comprise a detectable marker encased in at least two layers of carbon, wherein upon administration of said reagent said particles are dispersed in an aqueous medium and form a stable colloid;

binding [at least some of] said particles to said fibrin; and

detecting the presence of said detectable marker in said [fibrin-containing source] sample containing fibrin.

41. (Once amended) A detectable reagent for use in *in vivo* or *in vitro* detection of fibrin, said detectable reagent comprising discrete particles dispersed in a carrier, diluent, excipient, adjuvant or any combination thereof, wherein [at least some of] said particles comprise a detectable marker encased in at least two layers of carbon, wherein [at least some of] said particles preferentially bind to fibrin over other blood plasma proteins and wherein upon administration of said reagent, said particles are dispersed in an aqueous medium and form a stable colloid.

42. (Once amended) The detectable reagent according to claim 41, wherein each of said particles comprises a detectable marker encased in from 2 to 10 layers of graphitic carbon, at least an outer layer of said layers being chemically modified to [enable a stable] provide improved chemical association of the modified layers with aqueous solution relative to non-modified layers, thereby forming a stable aqueous colloid.

50. (Once Amended) The method of targeting a drug to a localized fibrin site *in vivo*, the method comprising the steps of:

administering to a patient an effective amount of a reagent comprising discrete particles dispersed in a veterinarily or pharmaceutically acceptable carrier, diluent, excipient, adjuvant or any combination thereof, wherein [at least some of] said particles comprise at least two layers of carbon and [at least some particles] have coupled thereto a drug to be targeted to the localized fibrin site, wherein upon administration of said reagent said particles are dispersed in an aqueous medium and form a stable colloid; and

binding [at least some] of said particles to said localized fibrin site;

whereby said drug is targeted to said localized fibrin site.

61. (Once amended) The method according to claim 31, wherein a surface of said particles is coated with a surfactant coating that increases the binding efficiency of said coated particles with fibrin relative to uncoated particles.

62. (Once amended) The method according to claim 32, wherein a surface of said particles is coated with a surfactant coating that increases the binding efficiency of said coated particles with fibrin relative to uncoated particles.

63. (Once amended) The detectable reagent of claim 41, wherein a surface of said particles is coated with a surfactant coating that increases the binding efficiency of said coated particles with fibrin relative to uncoated particles.